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Outcome in 43 Children Presenting With Metastatic Ewing Sarcoma: The St. Jude Children's Research Hospital Experience, 1962 to 1992

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The purpose of this work was to review the St. Jude Children's Research Hospital experience of patients presenting with metastatic Ewing sarcoma over a 30-year period. Forty-three of 212 cases of Ewing sarcoma presented with metastases at diagnosis. These patients were analyzed to determine whether primary tumor site or size, metastatic site(s), or advances in therapy have had a positive impact on survival. The overall survival for our 43 patients was 35% (95% confidence intervals, 20% to 50%). Comparing patients treated prior to 1979 with those treated after 1979, the overall survival was significantly different ($P = 0.0002$). Comparing overall survival between pelvic and nonpelvic primaries ($P = 0.24$), among metastatic sites ($P = 0.83$), and between tumors measuring >8 cm in diameter to tumors measuring <8 cm in diameter ($P = 0.12$), no significant differences were observed.

Approximately one-third of patients presenting with metastatic Ewing sarcoma may achieve long-term survival. Children with metastatic Ewing sarcoma may benefit from clinical trials which intensify the doses of doxorubicin, and the highly effective combination of ifosfamide/etoposide.

Key words: Ewing sarcoma, metastases, chemotherapy, radiation therapy

INTRODUCTION

Ewing sarcoma is a malignant undifferentiated tumor arising most often in bone and less commonly in soft tissues. Initially thought to be of endothelial origin (diffuse endothelioma of bone) [1], current clinical [2] and experimental [3] evidence points toward a primitive neural tissue origin. With modern multimodality therapy, 40–70% of children with localized Ewing sarcoma are surviving at 5 years [4–13]. However, a contemporaneous group of children with metastases at diagnosis fared substantially worse, with only 18–30% surviving at 5 years [14–17]. The prognosis is even less favorable for those patients with primary tumors >8 cm in diameter [14] and bone metastases at diagnosis [15].

We have reviewed and reanalyzed [7,14] 43 cases of metastatic Ewing sarcoma treated over a 30-year period at this institution to determine whether primary tumor site or size, metastatic site(s), or advances in therapy have had an impact on survival.

PATIENTS AND METHODS

From March 1962 to January 1992, 212 patients with Ewing sarcoma were treated at St. Jude Children's Research Hospital. Forty-three of these 212 patients had bone primary Ewing sarcoma (ES) with metastases at diagnosis. Contemporaneous review of all 43 cases were performed by one pathologist (D.A.P.) to ensure consistency in the diagnosis. All patients had histologically undifferentiated small, round-cell neoplasms without histologic, cytologic, or ultrastructural evidence consistent with lymphoma, neuroblastoma, or rhabdomyosarcoma. One sacral tumor had dense core granules and microtubules present on electron microscopy.

Evaluation for metastases at the time of diagnosis included the available diagnostic imaging techniques of the

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time including plain chest radiographs, skeletal survey, computerized tomography (CT), magnetic resonance (MR) imaging, and bone scans and bone marrow aspirates.

The 43 patients, all younger than 22 years, were enrolled on primary treatment programs as follows: pre-EWI-79 (n = 13 protocol patients admitted 5/62 to 11/78); EWI-79 (n = 18, protocol patients admitted 5/79 to 4/87) [18]; and EWI-87 (n = 12, protocol patients admitted 10/87 to 1/92) [19]. Patients who failed primary therapy were treated on available protocols, including Phase I and Phase II studies. Informed consent was obtained from patients, parents, or legal guardians, as appropriate. All protocols were approved by the Institutional Review Board.

TREATMENT

Prior to the initiation of our EWI-79 protocol, which is described below, patients received either single agent (cyclophosphamide, vincristine, dactinomycin, doxorubicin, or bleomycin) or multiagent combination chemotherapy. All patients received radiation therapy (RT) to the primary and/or metastatic site(s), and three underwent thoracotomy.

EWI-79 Protocol

This protocol comprised five courses of sequential cyclophosphamide, 150 mg/m^2/day orally, for 7 days followed on day 8 by doxorubicin, 35 mg/m^2 i.v. Local control was attempted at week 12. Radiation therapy was delivered as follows: 3,000–3,500 cGy for incomplete bone resections or biopsies with only microscopic residual disease, and 5,000 cGy for gross residual tumor. No pulmonary RT was given. Maintenance chemotherapy consisted of vincristine 1.5 mg/m^2/week for 11 doses, dactinomycin 1.5 mg/m^2 every other week for 6 doses, and six additional courses of sequential cyclophosphamide and doxorubicin followed by repetition of the vincristine (11 doses)/dactinomycin (6 doses) phase. The first 10 patients enrolled also received 1,3-bis(chloroethyl)-1-nitrosourea 50 mg/m^2 twice at 6-week intervals during the maintenance/continuation phase of therapy [18]. In all, 18 patients were enrolled in this study in 8 years.

EWI-87 Protocol

In this protocol all patients received a "window therapy" of ifosfamide 1.6 m/m^2/day and etoposide 100 mg/m^2/day, as three 5-day cycles. Mesna uroprotection was given immediately and at 3 and 6 hours after ifosfamide infusion. The evaluation of ifosfamide/etoposide was followed by three cycles of sequential cyclophosphamide and doxorubicin as given in the EWI-79 protocol. Patients with primary tumors <8 cm and those with resected tumors that had positive margins received 3,500 to 3,600 cGy of radiation therapy. Larger tumors received 6,000 cGy in twice-daily fractions of 120 cGy. Osseous metastatic lesions received 3,600 cGy unless the sites were too numerous to reasonably irradiate. Maintenance chemotherapy consisted of alternating courses of ifosfamide/etoposide and cyclophosphamide/doxorubicin plus vincristine and dactinomycin [19]. Twelve patients were enrolled on this study in 5 years.

STATISTICAL ANALYSIS

Survival time was measured from the date of diagnosis, with patients who were alive at last follow-up being censored. Disease-free survival was measured from the date of diagnosis to the date of first relapse. The duration of survival and disease-free survival was estimated using the method of Kaplan and Meier [20]. Ninety-five percent confidence intervals were obtained from Peto-Pike method [21]. Comparisons between different groups of primary sites and metastatic sites were made using the log-rank test [22].

RESULTS

Of 212 patients treated for Ewing sarcoma at St. Jude Children's Research Hospital between 1962 and 1992, 43 (20%) presented with metastases at diagnosis. The median age of these 43 patients was 12.8 years (range 3.6 to 22 years). Twenty-five of the patients were male. The majority were Caucasian (n = 41); two were African-American. Eighteen patients (42%) had pelvic primary tumors, 12 (28%) had long bone primary tumors, and 13 (30%) had flat bone primary tumors. Eighteen patients had only lung metastases; nine had bone metastases (one long, three flat, and five combined); five had bone and bone marrow metastases, four had lung and bone metastases; three had pleural metastases; and one each had bone marrow plus bone plus lung metastases, bone plus pleural metastases, inguinal lymph node plus lung metastases, and axillary lymph node metastases only. Of the 18 patients with lung metastases, four were detected only by CT, ten by both chest radiographs and CT, and four by chest x-ray alone prior to the availability of CT.

The overall survival of these 43 patients at four years was 35%, 95% confidence intervals 20% to 50% (Fig. 1). All patients treated prior to EWI-79 have died. When comparing the patients treated prior to EWI-79 with those treated on EWI-79 and EWI-87, the overall survival was significantly different with a P value of 0.0002 (Fig. 2). For nine patients with metastatic Ewing sarcoma treated by the EWI-79 protocol, seven are surviving disease-free (Fig. 2). Patients treated on EWI-79 and EWI-87 had a projected overall survival of 50% (P = 0.25) at 8 and 3 years, respectively. When comparing survival between

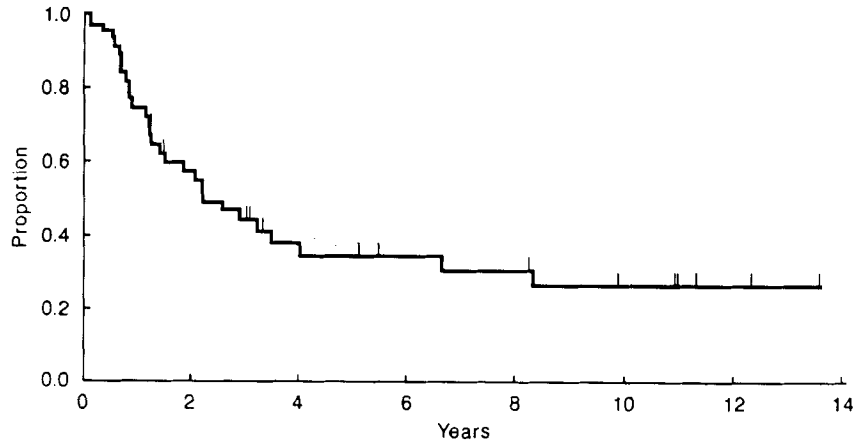

Fig. 1. Overall survival of children with metastatic Ewing sarcoma. Ticks represent censored times, i.e., times at which patients are still alive.

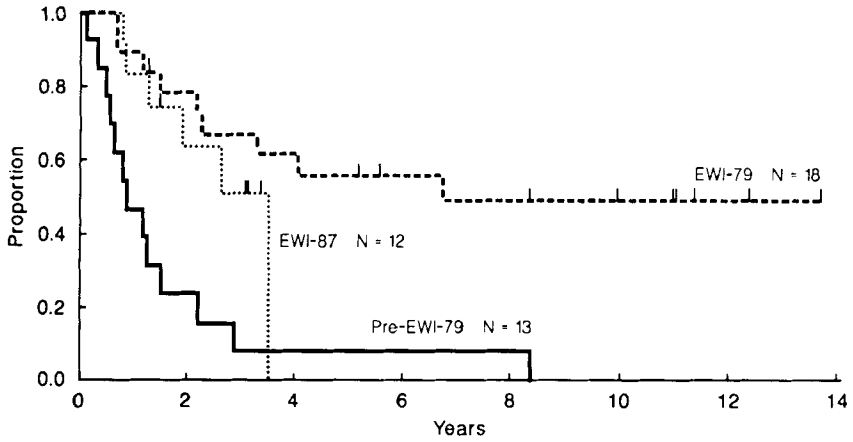

Fig. 2. Overall survival of children with metastatic Ewing sarcoma treated with pre-EWI-79, EWI-79, and EWI-87. Differences between pre EWI-79 and EWI-79/87 are significant ($P = 0.0002$).

pelvic and nonpelvic primaries ($P = 0.24$), among metastatic sites ($P = 0.83$), and between tumors measuring >8 cm and tumors measuring <8 cm ($P = 0.12$), no significant differences were observed (Table I). In our trial the addition of ifosfamide and etoposide decreased the dose intensity of cyclophosphamide and doxorubicin during induction (for cyclophosphamide 404 mg/m^2/wk to 186 mg/m^2/wk, for doxorubicin 13.5 mg/m^2/wk to 6.2 mg/m^2/wk).

TABLE I. Prognostic Data

Prognostic factor	Number of patients	Failures	*P* value*
Primary site			
Pelvic	18	10	0.24
Other	25	18	
Metastatic site			
Lung	18	12	0.83
Bone/BM[a]	14	9	
Multiple	11	7	
Tumor size			
<8 cm	9	3	0.12
>8 cm	23	14	

[a]BM, Bone marrow.
*Obtained by log rank test.

DISCUSSION

This report demonstrates that about one-third of patients with metastatic Ewing sarcoma at diagnosis may achieve long-term survival and be cured. Patients treated prior to 1979 had a poor outcome, with no long-term survivors. Many of these patients were treated with less aggressive therapy than is available today. Improvement in survival coincided with the initiation of the EWI-79

protocol and also the availability of new imaging technologies, including radionuclide scintigraphy and computed tomography. In 1983, encouraging early results for patients with metastatic Ewing sarcoma treated on the EWI-79 protocol were reported [18]. In March 1993, 15 patients were alive (follow-up 1.2–13.6 years) at a median follow-up of 5.6 years. The present report confirms that this tumor control has been durable. The 3-year survival rates are 61% (95% C.I 39–84%) and 51% (95% C.I. 19–83%) for patients on the EWI-79 and EWI-87 protocols, respectively. With small samples, no significant difference in the overall survivals between the two groups is found ($P = 0.25$). Similar outcome is noted for patients subsequently treated on the EWI-87 study which evaluated an experimental therapy of ifosfamide/etoposide. Although this two-drug combination is very active in retreatment of Ewing sarcoma, with 25 responses noted in 26 patients treated [19], we cannot detect a survival advantage for patients who presented with metastatic disease at diagnosis. Whether this two-drug combination improves the outcome for patients with Ewing sarcoma is unknown, and is presently being tested by the Intergroup Ewing Sarcoma Study.

Related to dose intensity, Smith et al. [23] performed a dose-intensity analysis of published Ewing sarcoma and osteogenic sarcoma trials to determine which agents were most closely associated with a favorable response. Their analysis suggested that doxorubicin dose intensity is an important determinant of favorable outcome in both cancers and that the dose intensities of other agents contributed less significantly to outcome.

The German Society of Pediatric Oncology studied 48 patients with metastatic Ewing sarcoma treated on two consecutive trials [16], Cooperative Ewing Sarcoma Studies (CESS) 81 and 86. CESS 86 differed from CESS 81 in that patients with tumor volumes >100 mL received ifosfamide with mesna uroprotection instead of cyclophosphamide. The disease-free survival (DFS) was 18% according to Kaplan-Meier life-table analysis after 7 years. Compared to patients with bone metastases, those with lung metastases alone who had surgical resection of the primary tumor and received pulmonary RT had a better rate of DFS (37% versus 12%, $P < 0.001$). We found no difference in overall survival among our groups of patients with metastatic Ewing sarcoma. Since our patients did not receive pulmonary RT, the impact of this therapeutic modality could not be assessed.

Three groups have evaluated the impact of consolidation with total body irradiation (TBI) and myeloablative chemotherapy followed by hematopoietic rescue in poor risk ES patients [5,24,25]. Miser et al. [5] studied 13 previously untreated patients with metastatic ES with an intensified regimen of vincristine, doxorubicin, and cyclophosphamide in combination with RT to the primary site (>5,000 cGy) and to osseous metastases (4,500 to 5,000 cGy). This was followed by one additional cycle of chemotherapy, TBI, and autologous bone marrow rescue (ABMR). Nine of the 13 patients relapsed, giving an event-free survival of 17% and an overall survival of 56% at 30 months.

Marcus et al. [24] evaluated two regimens for high-risk (HR) Ewing sarcoma patients (defined as those with tumors >8 cm or metastases at diagnosis): HR-2 (n = 10; 4 with metastases) consisted of conventional chemotherapy for 37 weeks followed by fractionated melphalan 60 mg/m^2/day for 3 days and ABMR; HR-3 (n = 10; 3 with metastases) consisted of intensified chemotherapy for 16 weeks followed by TBI (400 cGy on two consecutive days), cyclophosphamide, doxorubicin, vincristine, and ABMR. The 2-year DFS was 20% for HR-2 and 80% for HR-3. Of the seven patients with metastases only two patients with lung metastases treated with HR-3 are disease-free. Measurement of the impact of these studies is limited by the small number of patients with metastatic Ewing sarcoma enrolled and the short follow-up time [5,24].

Burdach et al. [25] studied 17 patients with poor prognosis Ewing sarcoma (defined as metastatic disease or relapse within 2 years of diagnosis). Thirteen patients received ABMR and four patients received allografts. The myeloablative regimen consisted of 1,200 cGy hyperfractionated TBI (2 × 150 cGy/day) plus melphalan 30 to 45 mg/m^2/day on 4 consecutive days followed by one dose of etoposide (40 to 60 mg/m^2). Event-free survival was 53% at 5 years for the transplant group compared to 2% for historical controls. Interestingly, no relapses occurred in the four patients who received allografts, compared to eight relapses in 13 patients who received ABMT. A pilot study was then conducted to determine whether Interleukin-2 could induce anti-tumor mediators and thus improve the outcome for those patients receiving ABMR. Only one of five patients treated with Interleukin-2 relapsed (median observation period 2 years) compared to five of eight patients not treated with Interleukin-2 (median observation period 1 year). These authors concluded that myeloablative therapy followed by autologous or allogeneic hematopoietic rescue can improve the survival for patients with poor risk Ewing sarcoma. These authors also suggest that further improvement may be achieved by exploiting immunologic anti-tumor mechanisms rather than by escalating cytotoxic radiochemotherapy [25].

Both Burdach et al. [26] and Miser's group [27] have updated their preliminary results [5,25]. The extensive reanalyses of their early conclusions are confirmed in these more recent reports. The study patients of Burdach et al. [25] have a relapse-free survival of 45% ± 12% at 6 years after the last event before transplant, compared

with 2% ± 2% for the historical control group. Miser's group has demonstrated that consolidation with myeloablative chemoradiotherapy failed to improve the outcome for patients with metastatic Ewing sarcoma [26]. Randomized trials must be performed before myeloablative therapy with hematopoietic rescue can be recommended for such patients.

Although an earlier report [14] from our institution concluding that the size of the primary tumor had an influence on outcome in patients who present with metastatic Ewing sarcoma, our reanalysis fails to support that contention. In fact, we did not observe any factors that had a positive impact on survival. The 4-year survival for all of our patients with metastatic Ewing sarcoma is 35% (95% C.I. 20–50%). Patients treated after 1979 have a 4-year survival of 52% (95% C.I. 31–70%).

We are now intensifying the doses of cyclophosphamide, doxorubicin, etoposide, and ifosfamide in a study for all patients with Ewing sarcoma. Children with metastatic Ewing sarcoma may benefit from this therapeutic endeavor.

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